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Review Article

ISSUES OF CONCERN REGARDING THE USE OF HYPERTONIC/ HYPERONCOTIC FLUID RESUSCITATION OF HEMORRHAGIC HYPOTENSION

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ABSTRACT—Small volume resuscitation fluids continue to be of interest to the military and limited volume resuscitation is becoming more common in the treatment of hemorrhage in the civilian community. With renewed interest to undertake a large US-Canada multi-center clinical trial of hypertonic saline alone or combined with dextran (HSD) possibly in 2006, concerns related to the safe use of this product continue to surface. This review addresses the use of these products in uncontrolled hemorrhage models, in dehydration and addresses perceived risks associated with hypernatremia, dextran-associated anaphylactoid reactions and effects on coagulation and renal function.

KEYWORDS—Hypertonic saline, hypertonic saline dextran (HSD), hemorrhage, dehydration, anaphylactoid reactions

The initial treatment of trauma-induced hemorrhage often requires fluid resuscitation to replace intravascular blood and plasma volume lost due to injury. Clinical practices have advocated early, aggressive fluid resuscitation in order to restore vascular volume and with it, restoration of organ perfusion. However, commonly in the urban pre-hospital setting, short transport times do not allow for sufficient administration of conventional fluids. These limitations become even more severe in the military setting where logistic constraints preclude the availability of large volumes of fluid. Moreover, mounting evidence from studies in experimental animals and trauma patients questions the prudence of rapid, aggressive restoration of arterial pressure in the face of continuing hemorrhage and possibly disrupting the required thrombi to fill the defect (1–4). Therefore fluid resuscitation tailored to the needs of the individual trauma casualty and to the time available for fluid administration has been advocated, and includes the concept of small volume or limited fluid resuscitation.

For many years the military has been interested in small volume resuscitation through the use of concentrated hypertonic fluids, such as hypertonic saline (e.g., 7.5% NaCl (HS)), which may be augmented with colloids such as dextran or hetastarch. In fact, several reviews of both human clinical trials and animal studies concluded that hypertonic and/or hyperoncotic resuscitation solutions are safe and potentially efficacious compared with isotonic crystalloid therapy (4–10). Perhaps the fluid most often investigated is 7.5% NaCl/6% Dextran-70 (HSD), though variants of this formulation have also been used. The benefit of such fluid therapy is that the hypertonic fluid rapidly augments physiologic transcapillary refill by drawing water from the tissues into the vascular space to promote tissue blood flow. This rapid fluid augmentation would eventually reverse itself, based on Starling forces in the microvasculature, but the addition of a large molecular weight colloid retains the translocated fluid in the vascular space for prolonged periods of time. As a result of this vascular volume augmentation, blood pressure rises, cardiac output increases, and tissue perfusion is restored.

Pioneering work to demonstrate the potential of HSD-type fluids in initial fluid resuscitation of life-threatening hemorrhage was conducted by Maningas et al. (11). They demonstrated, in a rapid, 70% hemorrhage model with 100% mortality, that 11.5 mL/kg HSD was 100% effective in maintaining survival over the 4 day experimental period, whereas equal volumes of hypertonic saline or Dextran-70 alone were only partially effective, and an equal volume of isotonic saline was ineffective in preventing death. Subsequent studies showed similar benefit with as little as 4 mL/kg of HSD (12). Those initial studies have been repeated around the world, in varied formats with similar success.

In a variety of animal models employing numerous experimental designs, the benefits of hypertonic and/or hyperoncotic fluid following hemorrhagic hypotension have been amply demonstrated by improved hemodynamics and subsequent survival, when compared to isotonic formulations of equal volume. A review of these studies and the physiological benefit of HSD was published recently (13). In addition, the Resuscitation Outcome Consortium (ROC) recently selected HS and HSD as the first fluids for consideration for a US-Canada multicenter trauma trial that could begin in 2006. However, enthusiasm over the potential efficacy of fluids such as HSD has been muted by concerns of safety. Perceived risks include, among others: increased bleeding following hypertonic/hyperoncotic fluid resuscitation in the presence of uncontrolled hemorrhage, cellular or tissue dehydration, neurologic injury or permanent neurologic deficit from transient hypernatremia ($Na^+ \geq 160$ mEq/L), precipitation or exacerbation of acute renal failure, dextran-induced anaphylactoid

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TABLE 1. **Levels of evidence for references cited***

Issues of concern	Level of evidence	Reference number
Uncontrolled hemorrhage	1	33, 35, 36
	2	13, 34
	5	1, 3, 11, 12, 14–32
Dehydration	5	37–49
Hypernatremia and head injury	1	35, 53, 55
	2	54, 59, 72
	4	72
	5	50–52, 60–71, 73–76
Renal failure	1	81
	2	78
	4	77
	5	79, 80
Dextran-associated anaphylactoid reactions	1	96
	2	84, 85, 88, 91–94, 97
	3	87, 90, 94, 100
	4	82, 83, 86
	5	89, 95, 99, 101–105
Repeated doses	5	106–108

*Levels of evidence adapted with permission from Center for Evidence-Based Medicine, http://www.cebm.net/levels-of-evidence.asp.
1) Systematic reviews, meta-analyses, randomized clinical trials; 2) Cohort studies, outcome research, systematic reviews of such studies; 3) Case control studies and systematic reviews of such studies; 4) Case series; 5) Preclinical research or expert opinion.

reactions (DIAR), dextran-associated coagulopathy and interference with cross-matching of blood, and effects of repeated doses of hypertonic/hyperoncotic fluid resuscitation causing intravascular fluid overload, pulmonary edema, cardiac failure, metabolic acidosis, etc. This review considers each of these perceived risks, their validity and their threat relative to the potential benefit of hypertonic/hyperoncotic fluid therapy, with an emphasis on HSD. The levels of evidence for each reference cited in the topics covered are presented in Table 1.

Uncontrolled hemorrhage

Initial, pre-clinical experimentation with HSD resuscitation of controlled hemorrhage demonstrated great promise in resuscitating otherwise fatal, or life-threatening hemorrhage (11, 14–16). With the advent of experimental models of uncontrolled hemorrhage, caution has again been raised regarding the prudence of rapid, aggressive and complete restoration of arterial pressure, without concomitant definitive or surgical hemostasis (1, 17–19). This is reminiscent of earlier caution for the same clinical issues (20).

These authors have all stressed the wisdom of gaining hemostatic control and the risk of exacerbated or renewed hemorrhage upon rapid restoration of blood pressure. Animal studies have demonstrated rebleeding and higher mortality in life threatening, but otherwise non-fatal models of uncontrolled hemorrhage, following immediate infusion of large volumes of isotonic crystalloid or small volume HS or HSD infusion (17, 18, 21, 22). Krausz et al. (23) reported that the increased bleeding following HS infusion was related, at least in part, to the size of the injured blood vessel, while others found that these uncontrolled rat tail hemorrhage models could be affected by the type of anesthesia employed (24, 25). Nevertheless, Matsuoka et al. demonstrated a benefit of HS resuscitation of uncontrolled hemorrhage from a solid viscus (liver) injury, but they cautioned that models of large vessel hemorrhage may give different results than solid organ hemorrhage (19, 26). For example, Leppaniemi et al. demonstrated benefit of early fluid resuscitation from aortic injury in rats, but HS resuscitation was not effective in their model (27).

In an earlier study by Matsuoka et al., HS was significantly more effective than other hypertonic fluids (Isosal, hypertonic acetate) or lactated Ringer's (LR) solution when used to resuscitate uncontrolled hemorrhage rom liver laceration in rats, even though HS was associated with a higher intraperitoneal hemorrhage volume (25.5 mL/kg vs. 22.5 mL/kg) (3). However, the isotonic solution was administered in equal volumes to the hypertonic solution (4 mL/kg), which is much lower than its usual dose for resuscitation (up to 22 mL/kg). Thus, equipotential volume resuscitation (i.e., 3 volumes of isotonic fluid for each volume of blood lost) may have resulted in greater intraperitoneal hemorrhage volumes for the isotonic solution and higher mortality rates. In fact, in a subsequent study by the same group, equipotential resuscitation of uncontrolled liver hemorrhage in rats demonstrated lower hemorrhage volumes and resuscitation fluid requirements for the hypertonic fluids than LR (19).

Nevertheless, studies have shown that a short delay before infusing any resuscitation fluid, or delivering it as a slow infusion rather than as a rapid bolus, improved perfusion of peripheral vascular beds, survival and lowered overall bleeding (22, 28–30). These observations were also supported by Elgjo and Knardahl who reported that in an uncontrolled vascular hemorrhage model in rats, increased bleeding was not observed, but hemodynamics were improved when the dose of HS was adjusted to 2 mL/kg (31). Most recently, Bruttig et al. demonstrated in swine that the rate of infusion was key to limiting rebleeding (32). At rates achievable through a standard IV set with a gravity feed, serious rebleeding was not observed. In addition, in several clinical trials utilizing HSD as a first fluid for resuscitation of penetrating trauma, no deaths have been attributed to its use. In fact, in the USA multicenter clinical trial of HSD, although not statistically significant, mean survival rates were 88% in patients with penetrating trauma who received HSD, but 77% in patients with similar injuries who received standard of care as isotonic crystalloid fluids (33, 34). No evidence of increased bleeding or greater blood requirements were observed in HSD-treated patients in any of the clinical trials, despite higher blood pressures in the HSD groups (35, 36). These differences between the clinical results and the animal studies may reflect the approximate 30 min or longer delay between injury and time of fluid administration in trauma patients.

Dehydration

Concerns have been raised that the use of hypertonic solutions would cause cellular or tissue dehydration sufficient

to damage or kill vital tissues, particularly those close to the site of administration; e.g. red blood cells, leukocytes or endothelial cells (37, 38). Moon et al. demonstrated in a rat model that, as previously thought, intracellular water was the source for water mobilization by hypertonic and/or hyperoncotic resuscitation fluids (39). Total body water did not change. Similar results were obtained by Saxe et al. using a canine modified Wigger's model of controlled hemorrhagic hypotension (37). As a result, in vivo and in vitro studies were conducted to clarify the concerns regarding cellular shrinkage and dehydration. Incubation of pig, rabbit or human red blood cells (RBCs) with HSD or its components, HS or Dextran-70, revealed minimal changes in RBC morphology and no Rouleaux formation (38, 40). In addition, infusion of HSD at 4 mL/kg induced no morphologic changes in rabbit RBCs (38). Toxicological evaluation of the irritation potential of HSD and its components, HS and dextran-70, concluded that a standard 4 mL/kg dose of HSD infused into a peripheral or central vein should not induce any greater inflammation of the vein than LR (41). If, however, significant extravasation of hypertonic fluid occurred, the potential for localized, focal necrosis of the tissue increased.

Recent evidence from large animal hemorrhage experiments confirmed that dehydration compromised recovery from hemorrhage and reduced survival (Table 2) (42, 43). Krausz et al. and Sondeen, et al. also reported that dehydration compromises the ability to tolerate hemorrhage (44, 45). Nevertheless, in these studies of moderate hemorrhage in dehydrated animals, the hemodynamic efficacy of HSD resuscitation was not impaired (Table 2) and there were no reports of untoward effects (42, 45–47). For example, considering the hypernatremia associated with dehydration, HSD infusion did not raise plasma Na^+ concentrations to dangerously high levels (45). Similar findings were observed by Krausz et al. following HS infusion in dehydrated rats (44). In addition, in one study, resuscitation with HSD extended survival times (43). There was no report of differential compromise of physiological function in these experiments, indicating that none of the resuscitation solutions represented a hazard to post-resuscitation performance. It should also be noted that 4 ml/kg of HSD was more effective in rats and pigs than a similar dose of normal saline in restoring plasma volume following moderate dehydration in the presence or absence of hyperthermia (48, 49). The implication is that HSD could be effective in the acute therapy of hyperthermia or dehydration until standard isotonic fluid replacement was possible.

TABLE 2. **Survival in hemorrhaged, dehydrated swine treated with HSD**

	Wade et al. (42)		McKirnan et al. (46)		Alemayehu et al. (43)	
Group	n	% Survival	n	% Survival	n	Survival time (min)‡
Euhydrated	5	100	7	100	7	159 ± 10§
Dehydrated	4	0	8	50	7	107 ± 12
Dehydrated + HSD*	12	58§	13	92.3§	8	133 ± 10
Dehydrated + LR†	–	–	11	90.9	–	–

*7.5% NaCl, 6% Dextran–70, 4mL/kg.
†Lactated Ringer, 33.3 mL/kg.
‡Mean ± SEM.
§$P < 0.05$ from dehydrated group.

Hypernatremia and Head Injury. Neurologic injury or permanent neurologic deficit from transient hypernatremia ($Na^+ \geq 160$ mEq/L)

Previous studies in euvolemic experimental animals showed that HSD infusion raised plasma Na^+ concentrations in a dose dependent manner (50). At the recommended dose of 4 ml/kg body weight, HSD transiently raises plasma Na^+ about 12–15 mEq/L. In some experiments plasma Na^+ exceeded 160 mEq/L, but again these concentrations were transient, and have not been associated with overt behaviors suggestive of toxicity (51). In dogs infused with 20 ml/kg HSD or HS daily for 14 days (i.e., 5 times the recommended therapeutic single dose), overt behavioral signs of toxicity were observed immediately after infusion and began to subside by 1 h (52). It is possible that some of these behaviors may relate to a hypernatremia, but peak plasma Na^+ concentrations were not determined. However, Na^+ concentrations were normal each day prior to the infusions (52). In general, elevations in plasma Na^+ concentrations observed in experimental animals after infusion of therapeutic doses of HSD, are similar to the Na^+ concentrations observed in trauma patients (53, 54). In addition, in a clinical trial in dogs, serum Na^+ concentrations were not significantly higher in HSD than LR treated animals (55).

There has been long-standing concern that plasma Na^+ concentrations in excess of 160 mEq/L will cause acute neurologic damage or permanent neurologic deficit and continued clinical concerns identify the use of HSD with this risk. To date, no documented neurologic damage or deficit, such as seizures or central pontine myelinolysis have been attributable to HS or HSD in humans (53, 56, 57).

To the contrary, studies in experimental animals and humans suggest that HSD may be highly effective in treating head injury, either alone or associated with hemorrhagic hypotension. It is appreciated that tissue swelling in a closed cranium threatens to cause major pressure-induced brain damage or death and that concomitant hemorrhagic hypotension reduces cerebral oxygen delivery resulting in a secondary ischemic insult; the consequence being nearly a 2-fold higher incidence of adverse outcomes in these patients with combined injuries (35, 58). Thus, the report that patients with traumatic brain injuries and hemorrhagic hypotension treated in the pre-hospital setting with HSD, are twice as likely to survive to discharge than those patients treated with standard of care, has important implications (59).

Numerous studies have investigated possible mechanisms by which hypertonic/hyperoncotic resuscitation solutions may be effective in models of head injury and hemorrhage. Infusion of HS, either alone or combined with 10% Dextran 60, reduced the water content in non-injured portions of the brain and lowered the intracranial pressure, thus reducing cerebral edema (60–63). Although HS-hydroxyethylstarch also reduced intracranial pressure in a rabbit global ischemia model, pentastarch alone had no effect on brain water content in a similar model (64, 65).

In another study, Sheikh et al. (66) demonstrated essentially equal effects on hemodynamics and reductions in intracranial pressure when anesthetized sheep with combined head injury and hemorrhage were resuscitated with either HS or Isosal (a lower sodium content 2400 mOsm hypertonic fluid). Not surprisingly, Isosal was associated with lower plasma Na^+ levels than HS. Also, Berger et al. demonstrated equal potential to reduce intracranial pressure following cerebral injury (with an associated space-occupying lesion) for both hypertonic mannitol and HSD (67). However, systemic pressure tended to decrease following mannitol, while it rose beneficially with HSD.

At least some of the improvement observed with hypertonic/hyperoncotic fluids is attributable to higher mean arterial pressures and cerebral perfusion pressures, resulting in higher cerebral blood flow in HS, HSD, or HS-10% hydroxyethylstarch-treated animals compared with controls (58, 68–71). Hartl et al. presented a recent clinical demonstration in which the use of HS-hetastarch reduced intracranial pressure levels from 45 +/− 15 mmHg to 25 mmHg +/− 14 and increased cerebral perfusion pressures from 52 +/− 18 mmHg to 72 +/− 16 mmHg (72). At the same time, transient hypernatremia normalized in less than 30 min. In another study, Hartl et al. reported that in a traumatic brain injury model in rabbits, infusion of HS-10% Dextran 60 reduced white blood cell margination and prevented the secondary arteriolar diameter increases associated with the injury (73). It should also be mentioned that in a gerbil cerebral ischemia-reperfusion model, 2 ml/kg of 10% NaCl reduced neuronal cell death in the hippocampal CA1 region (74). In addition, Tuma et al., reported that HS infusion attenuated spinal cord injury in a rat model (75).Taken together, these observations support the conclusions of Walsh et al. that an advantage of HSD resuscitation of the head injured patient, is to provide the surgeon with sufficient time to effectively intervene and prevent the occurrence of secondary brain injury (71).

There are, of course, conflicting reports in the literature, as evidenced by a study by DeWitt et al., (76) who contend that hypertonic or hyperoncotic fluids did not improve cerebral oxygen delivery following traumatic brain injury and mild hemorrhage in cats. However, the critical resuscitation solutions were oncotic plus isotonic (10% hetastarch plus isotonic saline) or mild hypertonic saline (3%). Apparently to compensate for the reduced hypertonicity, the solutions were administered in volumes equal to the shed blood volume. While interesting and provocative, these studies are distinctly different from most studies with hypertonic and/or hyperoncotic resuscitation solutions which are considerably more concentrated, and which are administered in considerably smaller volumes.

Renal failure

Concern has been raised that with extremely low arterial pressure, as seen following life-threatening hemorrhage (a condition associated with a small but significant occurrence of acute renal failure), addition of a hypertonic/hyperoncotic resuscitation solution would dehydrate sensitized renal cellular structures and precipitate or exacerbate acute renal failure. This was of particular concern with HSD since dextran is primarily cleared by the kidney. A clinical report linked infusion of large doses of Dextran-40 to the precipitation of renal failure in an older patient, although early studies failed to observe any significant effect of dextran on renal function in patients or animals free of renal disease (77–79). Furthermore, Malcolm et al. also raised concern that HS infusion would adversely affect renal function in dehydrated, hemorrhaged rats (80). In a model of both food and water deprivation, and induction of hemorrhage and 25 min of renal artery occlusion induced by cross-clamping the renal artery, rats resuscitated with HS had reduced renal function and overall lower survival rates when compared with rats resuscitated with LR. However, dehydrated rats in the HS group were hemorrhaged to lower blood pressures than rats in the other groups, and no information was presented as to the degree of dehydration or the cause of death in these animals. Also, in a combined dehydration-hemorrhage sheep model, renal function was not affected by HSD infusion for the 2 wk experimental period (47). Whether differences in these studies reflect the added detriment of renal occlusion and/or the added benefit of dextran is unknown. Although the extent of dehydration in the trauma patients treated with HSD is unknown, the incidence of acute renal failure tended to be less in the HSD than the crystalloid-treated group (33, 81). Considering that the incidence of renal failure in today's ICUs is < 1%, this theoretical adverse effect of HSD seems of little concern.

Dextran-associated anaphylactoid reactions

Concern has been raised regarding the possibility of the development of severe allergic reactions to synthetic colloids, such as dextran. These reactions are associated with dextran-reactive antibodies (DRA) which are believed to be present in most humans in low titers. It is reported that the most serious dextran-induced anaphylactoid reactions (DIAR) are observed in patients with high DRA titers (82). Generally, only small volumes of dextran need to be infused to elicit a reaction and DIAR usually occurs in the first few minutes after infusion begins (57).

Historically, significant allergic reactions have been associated with dextrans of molecular weights >100,000 or those with a greater degree of branching than current clinical dextrans (83–85). In general, observations of severe DIARs to clinical dextrans with average molecular weights of 75,000 or less are considered rare, with incidences in the range of 0.013% to 0.024% (86, 87). The majority of these cases were in older elective surgery patients who received epidural or spinal anesthesia. In comparison to other colloids, the incidence of anaphylactoid reactions related to dextran are about twice the rate for albumin, whereas the incidence of these reactions due to hydroxyethyl starch or gelatin is 2-fold and 6-fold higher, respectively, than for dextran (88).

Based on the proposed mechanism associated with DIARs, Promit (Dextran 1, MW 1000) was introduced to reduce the incidence of severe reactions (89). A 10 year study in Sweden reported a 35-fold reduction in the incidence of severe DIARs and a 90-fold reduction in DIAR-associated deaths (89). Promit had no effect on mild DIAR. It was concluded that use of Promit just prior to infusion of dextran solutions in patients of any type, is considered to make dextran one of the safest colloids to use (90).

The question has been raised as to whether Promit should be required prior to infusion of HSD in trauma patients. It should be noted that the full 20 ml dose of Promit should be infused IV about 1–2 minutes, but not longer than 15 minutes prior to infusion of HSD. It has been previously reported that mixing Promit into the HSD preparation was not as effective in reducing the incidence of DIARs as prior infusion and the full 20 ml dose in adults was much more effective than 10 ml (91, 92).

Finally, it should be noted that use of Dextran-1 was not without risk. Side effects associated with its use are considered mild and have included skin reactions, bradycardia and hypotension, i.e., some of the conditions for which HSD is used to treat in trauma patients (91–94).

To date with over 800 trauma patients enrolled in clinical trials receiving HSD and over 20,000 trauma patients having received RescueFlow (HSD) in Europe, no incidences of DIARs have been reported (57; Biophausia, personal communication, 2005). Laubenthal et al. reported that use of Promit 1 was unnecessary in trauma patients (95). It has been suggested that elevated catecholamine levels in trauma patients may be protective from development of DIARs in trauma patients (96, 57). In addition, the rapid infusion of HSD may result in excess antigen in blood that prevents immune complex formation. Whatever the mechanism, it is medical opinion that trauma patients seem to be protected from development of severe DIAR. It should be noted that the Swedish Physician's Desk Reference makes no recommendation for using Promit in trauma patients (57).

From the clinical experience with the use of hypertonic hetastarch (HHS) in Austria, it was observed that 3 of 4 adverse events were attributed to anaphylactoid reactions with an estimate of 18,500–37,000 patients treated with 1–3 units (97). Patients were treated for hypovolemia in either the ICU or pre-hospital, but the number of actual trauma patients was not listed and it is not stated if the adverse events were in trauma patients (97). As a worse case scenario we could assume that these patients were trauma victims. The above data would translate to 5–6 anaphylactoid events per 100,000 units of HHS used or 8–16 per 100,000 patients. Since the incidence of such reactions with dextran is half that of hetastarch, an incidence rate of 0.004–0.008% could be possible. It should be noted that hydroxyethyl starch containing products such as Hextend and Hespan have been advocated for treating hypovolemia despite the known risk for anaphylactoid reactions that is greater than that for dextran.

Dextran-associated coagulopathy

Several studies have shown that high doses of high molecular weight dextrans interfere with proper blood coagulation schemes (98, 99). As a result, concern has been raised that the use of HSD-type resuscitation fluids would interfere with coagulation at a time when coagulation was most needed; i.e., following massive hemorrhage or tissue trauma. However, studies in experimental animals failed to detect significant effects on bleeding time, platelet aggregation or coagulation (100). Although a transient prolongation of prothrombin time was observed, the effect was attributable to HS (101, 102). Others have also observed prolongation of prothrombin time or thrombin time in human blood incubated with HS or HSD at concentrations of at least 10% (103, 104). For the most part these significant effects are observed at concentrations higher than believed would be observed in surviving patients treated with the recommended dose of 4 ml/kg HSD (105). In addition, in the clinical trials completed to date, PT and PTT were similar among patients treated with crystalloids, HSD, 7.5% NaCl containing 6 or 12% Dextran-70 or HS (32, 33, 36). No coagulopathy has been reported in any trauma patient treated with HSD. In addition, HSD treatment of trauma patients did not interfere with cross-matching of blood, a finding consistent with observations in human blood in vitro (33, 40).

Repeated doses

There is concern that HSD will have serious side effects if used in large doses, i.e., in a similar fashion to isotonic resuscitation fluids. Therefore, it is important to properly train personnel as to the most efficient usage of hypertonic/hyperoncotic solutions. However, only a few studies to date have examined the limitations of this therapy in the resuscitation of hemorrhagic hypovolemia. Employing a swine model of repeated cycles of rapid hemorrhage and immediate HSD resuscitation, O'Benar, et al. (106) reported that in this scenario, more than 2 doses of 4 ml/kg HSD was without further hemodynamic benefit in a situation where hematocrit was reduced to 8%. In a pressure-driven hemorrhage model, Prist et al. (107) noted that a second dose of HSD given 30 min after the initial dose and with continuous LR infusion did not offer any hemodynamic advantage, but lowered hematocrits to 12.6%. Therefore, based on these severe hemorrhage models, it would seem prudent to not recommend administering more than 2 doses of HSD within a short period of time in the presence of continued bleeding. However, since daily doses of HSD at up to 4 or 5 times the recommended therapeutic dose for 14 d was well tolerated in rabbits and dogs (52, 108), it would appear that multiple doses of HSD could be safe and effective when titrated to the needs of the individual patient.

SUMMARY AND CONCLUSIONS

This review has considered many of the issues of concern regarding the use of hypertonic and/or hyperoncotic resuscitation solutions as treatments for hemorrhagic hypotension following penetrating or blunt trauma. As discussed, no treatment is without risk, but there are some significant benefits derived from the use of small volume solutions for full or limited resuscitation, especially in austere pre-hospital settings. However, the optimal resuscitation fluid or regimen has yet to be defined. Several different options may be required for effective treatment. Healthcare delivery personnel from first responders to definitive surgeons must constantly assess the situation and perform (or not) those treatments expected to benefit the individual patient. With specific reference to fluid resuscitation, the studies of Saxe et al. (37) among others serve to show that HS and HSD type solutions have primary benefit as the initial resuscitation solution by rapidly expanding plasma volume and improving hemodynamics, thereby extending the therapeutic window

until the patient can be transported to a definitive treatment center. Subsequent resuscitation should be titrated to desired physiological and metabolic performance objectives in a definitive care environment.

On balance, HSD-type resuscitation solutions, like other resuscitation solutions, are not without potential risk, but to date, data from the clinical trials suggest minimal risk (33, 36, 53–55). Complications have been ascribed to the trauma incurred and none have been related to treatment with HSD or other hypertonic/hyperoncotic solutions. Where time is critical and resuscitation fluids are required, the observed benefits of HSD administration appear to outweigh any perceived risk and small volume resuscitation may mean the difference between life and death. But like any other therapeutic option, judgment must be used in its application to specific patients. "Do no further harm" must still be a guiding principle, but "do that which is most effective" is the most useful corollary.

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